Central Cardiovascular Effects of *Alpha* Adrenergic Drugs: Differences between Catecholamines and Imidazolines

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ABSTRACT

To check whether the central hypotensive effect of *alpha* adrenergic agonists is linked with the stimulation of *alpha*-2 receptors, such drugs were administered directly to the nucleus reticularis lateralis, which is an important site for the hypotensive action of clonidine. These experiments were carried out by microinjections (0.5 µl on each side) in normotensive cats anesthetized with pentobarbital. α-Methylnorepinephrine, a selective *alpha*-2 agonist (0.1–10 µg/kg) had no hypotensive effect in this region, whereas potent *alpha*-1 agonists such as cirazoline (0.01–1 µg/ kg) and ST 587 (1–10 µg/kg), like clonidine, produced do dependent hypotensive effects. Our results suggest that *alp* 2 selective catecholamines are not active in the nucleus reti laris lateralis region, whereas imidazolines induce a hypotens effect whatever their affinity for one subtype of *alpha* adrenoc tors. Therefore, there may be some form of structure-activ relationship which would indicate the existence, in this particu region of the medulla oblongata, of sites preferring the imida line structure.

Based in particular on antagonism experiments with yohimbine and piperoxan, the central hypotensive effect of substances such as clonidine and α-MNE is usually attributed to their selectivity for noradrenergic receptors of the *alpha*-2 subtype (for review see Schmitt, 1977; Berthelsen and Pettinger, 1977; Starke, 1981; Timmermans and Van Zwieten, 1982). Because α-methylparatyrosine, reserpine, and 6-hydroxydopamine do not usually affect the hypotensive effect of clonidine and α-MNE, these *alpha*-2 adrenoceptors are generally thought to be located postsynaptically (Finch, 1975; Kobinger and Pichler, 1976; Schmitt, 1977; Kobinger, 1978; Kubo and Misu, 1981). The hypothesis of a hypotensive effect linked with the stimulation of the *alpha*-2 adrenoceptors within the brain would imply that all selective *alpha*-2 agonists decrease the arterial blood pressure when administered directly to the action site of one of them, for instance that of clonidine.

Conversely, the agonists with opposite selectivity (maximum for *alpha*-1 adrenoceptors and minimum for *alpha*-2 adrenoceptors) might be expected not to have the same effects. To verify these hypotheses, we compared the effects of selective *alpha*-2 agonists such as α-MNE with those of *alpha*-1 agonists such as cirazoline and ST 587. We choose α-MNE because it is one among the most *alpha*-2 selective agonists in isolated organs as well in binding assays (Starke *et al.*, 1975; Langer, 1980; Rouot *et al.*, 1982). Starke *et al.*, (1975), for instance, reported that α-MNE is the most potent agent in reducing the norepinephrine

release in the rabbit pulmonary artery. It is therefore consider as a highly selective agonist for presynaptic *alpha*-2 recepto α-MNE is also the most selective ligand for *alpha*-2 recept in binding experiments performed on rat brain cortex (Rou *et al.*, 1982). In these experiments, the *alpha*-2/*alpha*-1 select ity was measured by the Ki ratio obtained by displacing [³ yohimbine as a ligand for *alpha*-2 receptors and [³H]prazo: as a ligand for *alpha*-1 receptors; this ratio is 7.69 for αMN Conversely, cirazoline and ST 587 are proposed as the m potent *alpha*-1 agonists, especially because their pharmacolo ical effects are mostly antagonized by prazosin, e.g., their ripheral vasoconstrictive effects (De Jonge *et al.*, 1981; Cav *et al.*, 1981; Ruffolo and Waddell, 1982; Beckeringh *et al.*, 198 In binding assays on cortical membranes, *alpha*-2/*alpha*-1 finity ratio (yohimbine sites/prazosin sites) is minimum cirazoline and ST 587. This indicates that these compoun are the most selective *alpha*-1 agonists yet available (Rouot al., 1982; B. Rouot, personal communication).

It is also interesting to note that these *alpha*-adrenergic dr belong to different chemical classes; catecholamines (α-MN and imidazolines (clonidine, cirazoline and ST 587; fig. Therefore, the structure-activity relationship aspect will a be discussed in this report.

In order to compare the cardiovascular effects of these *alp* adrenoceptor agonists to those of clonidine as a referen substance, we performed microinjections of all these substan in the NRL, which we characterized as a site of action clonidine (Bousquet and Guertzenstein, 1973; fig. 2). In fa we previously reported that the electrolytic lesion of this me

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ABBREVIATIONS: MNE, methylnorepinephrine; NRL, nucleus reticularis lateralis.

CLONIDINE

CIRAZOLINE
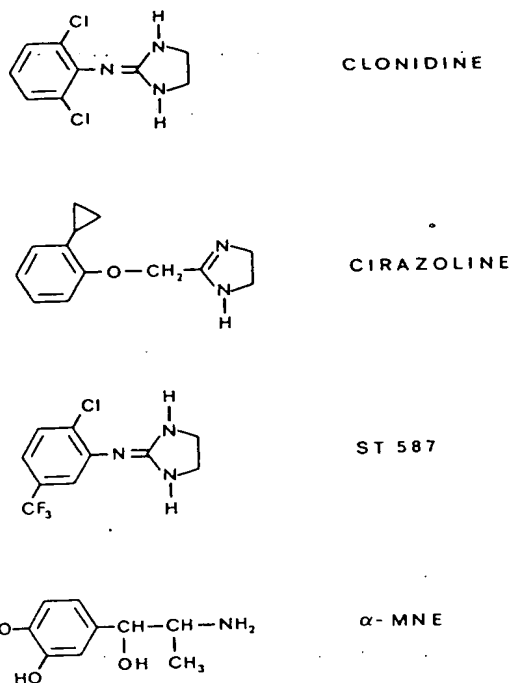
ST 587

α- MNE

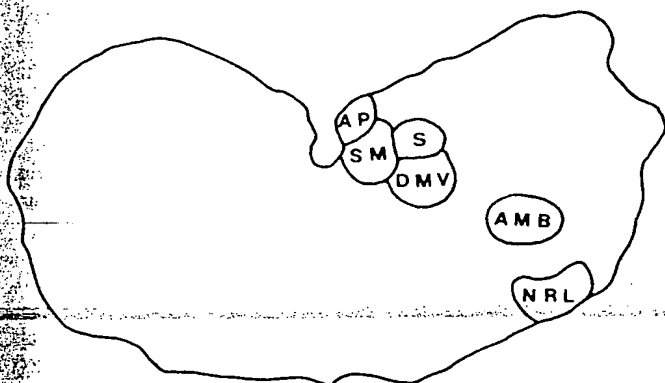**Fig. 1.** Chemical structures of the *alpha* adrenergic drugs injected into the NRL.

Fig. 2. Coronal section at the level of the obex of the brain stem of the cat passing through the medial part of the nucleus tractus solitarii (SM), the solitary tract (S), the dorsal motor nucleus of the vagus (DMV), the area postrema (AP), the nucleus ambiguus (AMB), and the nucleus reticularis lateralis (NRL) (Berman, 1968).

ullary region completely prevents the hypotensive effect of clonidine injected i.v. (Bousquet *et al.*, 1975). We also showed that the region of the NRL is highly sensitive to this substance because doses as low as 75 ng/kg produce here a significant hypotension when the drug is applied with the microinjection technique (Bousquet *et al.*, 1981).

Methods

Cats of either sex weighing 2 to 3.5 kg were anesthetized with pentobarbital (30 mg/kg i.p.). The animals were tracheotomized and artificially ventilated with a Bird Mark 8 ventilator. The animals were immobilized with pancuronium bromide (Pavulon) (2 mg/kg i.v.). The femoral artery and vein were cannulated for recording of systemic blood pressure and the injection of drugs, respectively. Blood pressure and heart rate were recorded with a Statham P23 Db transducer connected

to a Minipolygraph Gilson. The heart rate was monitored from the electrocardiogram with a cardiotachometer (IC-CT, Gilson Medical Electronics Inc., Middleton, WI).

Microinjection in the NRL region. Drug injections into the NRL were performed according to the method previously described by Bousquet *et al.*, (1980). The head of the animal was placed in a stereotaxic frame (La Précision Cinématographique Française, Ashières, France). To expose the doral surface of the medulla oblongata, the neck muscles were separated from the occipital protuberance and reclined downward. After removing the atlanto-occipital membrane the occipital bone was resected up to the protuberance and the dura mater was sectioned. At this stage, the two parallel glass needles (outer diameter, 150 μm, 7 mm apart) were positioned level with the obex at an angle of 23° to the horizontal. The needle tips were then inserted 8 to 8.5 mm into the medulla oblongata. They were connected to Hamilton microsyringes (10 μl) by means of polyethylene catheters. Slow injections (10 sec) were carried out by means of a micrometer.

Using the bilateral microinjection technique, we injected in the NRL very small volumes of drugs dissolved in 0.9% NaCl 0.5 μl on each side. The stereotaxic insertion of the needles in the brain stem sometimes produced transient cardiovascular responses. In these cases, the microinjections were carried out only when arterial pressure and heart rate had returned to initial values.

At the end of each experiment, Evans blue was injected into the NRL under exactly the same conditions as the drug solution. Then the brain was removed and fixed in 10% formalin. Subsequent histological verification on 50 μm frozen sections confirmed the desired location of needle tips and showed the diffusion of the stain around the point of injection.

Drugs. The following drugs were used in this study: 2-(2-chloro-5-trifluoromethyl-phenyl-imino)-imidazolidine nitrate (ST 587 NI, Boehringer Ingelheim Ltd., Elmsford, NY); 2-(2'-cyclopropyl phenoxymethyl)-imidazoline HCl (LD 3098: cirazoline, Laboratoire d'Etudes et Recherches Synthélabo, Paris, France); α-MNE (Hoechst, FRG); clonidine hydrochloride (Catapressan, Boehringer Ingelheim Ltd.); pentobarbital (Nembutal, Abbott Laboratories, North Chicago, IL); and pancuronium bromide (Pavulon, Organon Tecknica, France).

Statistics and calculations. Results are expressed as means ± S.E.M. The statistical significance was calculated by Student's t test for paired comparisons. $P < .05$ was set as the threshold of statistical significance.

Results

Effects of clonidine. Clonidine, as the reference substance, was injected into the NRL of four normotensive, anesthetized cats. The total dose of 0.1 μg/kg was injected bilaterally in a volume of 0.5 μl. The mean blood pressure decreased from 125 ± 10 to 110 ± 10 mm Hg ($P < .001$), *i.e.*, 12.5 ± 2%.

This hypotension was accompanied by a bradycardia of 10 ± 2.5% ($P < .05$). The cardiovascular effects began within 1 min of injection, lasted more than 30 min and were reversible (fig. 3; table 1). A total dose of 1 μg/kg produced a 25 ± 3% fall in blood pressure ($n = 4$; table 1). This effect was accompanied by a sustained bradycardia of 26 ± 7%. The cardiovascular effect of this dose of clonidine also began within 1 min of injection but lasted more than 60 min.

Effects of α-MNE. Bilateral microinjections of α-MNE (0.5 μl) were performed into the NRL of anesthetized cats. α-MNE was administered at total doses of 0.1, 1 and 10 μg/kg with four animals for each dose. Mean arterial pressures before the injections are given in table 1.

None of these doses of α-MNE ever significantly affected either the mean arterial pressure or the heart rate after 30 min observation (fig. 3; table 1). At the doses of 1 and 10 μg/kg, however, α-MNE sometimes produced a weak depressor effect
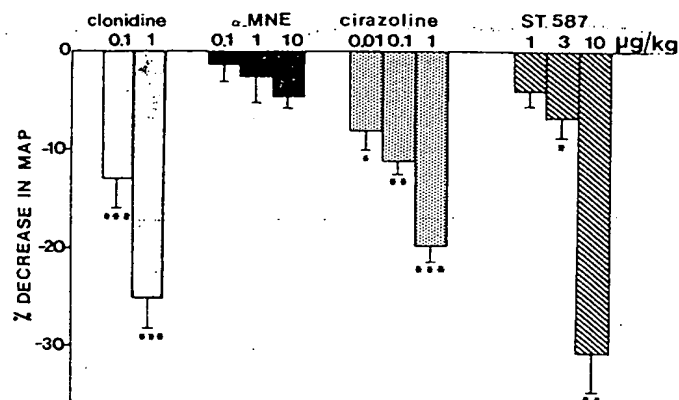
Fig. 3. Effects on the mean blood pressure (MAP) of various *alpha* adrenergic drugs injected bilaterally in the NRL of anesthetized normotensive cats ($n = 4$ for each dose). * $P < .05$; ** $P < .01$; *** $P < .001$.

that was on the average less than $5 \pm 1\%$. No bradycardia occurred even when blood pressure slightly decreased.

Effects of cirazoline. Microinjections of cirazoline at total doses of 0.01, 0.1 and 1 μg/kg were performed in anesthetized cats. Mean blood pressure and heart rate before injection, given in table 1, show that the initial values were similar in all series.

Cirazoline exhibited a dose-dependent hypotensive effect. Mean blood pressure decreased by $8 \pm 2\%$ after a dose of 0.01 μg/kg, $11 \pm 1\%$ after a dose of 0.1 and $19.5 \pm 1\%$ after a dose of 1 μg/kg (fig. 3; table 1).

This effect started within 1 min of injection. The duration of the effect depended on the dose; it lasted more than 30 min for the highest dose (1 μg/kg). This hypotensive effect was never accompanied by an significant change in heart rate. Nevertheless, we observed a weak bradycardia with the dose of 1 μg/kg. Decrease in heart rate was less than 5%. Thus, cirazoline elicited a depressor effect when injected into the NRL which was similar to that observed with clonidine injected the same way.

Effects of ST 587. ST 587 was administered under the same conditions at doses of 1, 3 and 10 μg/kg. We did not observe any significant hypotensive effect at the dose of 1 μg/kg. However, at doses of 3 and 10 μg/kg, ST 587 has hypotensive

effect not accompanied by any heart rate modification, as shown in figure 3 and table 1.

At the dose of 3 μg/kg, we observed a weak depressor effect with ST 587. Blood pressure fell by $6.5 \pm 2\%$. At the higher dose of 10 μg/kg, blood pressure decreased immediately after injection ($31 \pm 5\%$; $P < .01$).

At this dosage, the peak effect was reached within 10 min of injection and lasted more than 1 hr and was reversible. Therefore, ST 587 produced cardiovascular effects which were similar to those obtained with cirazoline when injected into the NRL. This drug, however, was less potent than the former. In fact, 3 μg/kg of ST 587 are needed in order to produce hypotensive effect similar to that obtained with 0.01 μg/kg of cirazoline.

Discussion

In an earlier study, we reported the high sensitivity of the NRL region to clonidine (Bousquet *et al.*, 1981). Microinjections of very low doses of clonidine at this level produce hypotension. The NRL is considered as a tonic vasopressive structure, a relay on the pathways of the baroreceptor reflex arc (Palkovits and Zaborszky, 1977). Here clonidine, as well as tetrodotoxin, inhibits an excitatory structure (Bousquet *et al.*, 1980). Other authors have, moreover, confirmed that a site for the central action of clonidine is located within the medullary lateral reticular formation. In fact, Sharma *et al.* (1978) and Cahusac and Hill (1983) reported an inhibitory effect of clonidine directly applied by means of microiontophoresis on excitatory cardiovascular neurons in the ventrolateral part of the brain stem. Chan and Koo (1978) and Wolf and Mohrland (1984) confirmed the existence of a ventromedullary site of action of clonidine in the rat. The microinjection of drugs into the NRL region was used as a means of analyzing the mechanism of hypotensive action of *alpha* adrenergic drugs. We first used α-MNE, a catecholamine shown to be one of the most selective *alpha*-2 agonists (see the introductory section). α-MNE is also of interest because it is reputedly the active metabolite of α-methyldopa (for review see Porter *et al.*, 1977). We report here that it has no hypotensive effect at any dose applied into the NRL region. This observation complements our previous findings that norepinephrine itself had no effect there (Bloch *et al.*, 1973; Bousquet and Schwartz, 1983). Fur-

TABLE 1

Effects on the mean blood pressure (MAP) and heart rate (HR) of the alpha adrenergic drugs microinjected into the NRL of normotensive anesthetized cats ($n = 4$ for each dose)

Drug	Dose	Before Injection		% Decrease After Injection	
		MAP	HR	MAP	HR
	μg/kg	mm Hg	beats/min	mm Hg	beats/min
Clonidine	0.1	125 ± 10	155 ± 9.5	12.5 ± 2***	10 ± 2.5*
	1	117 ± 6	163 ± 8	25 ± 3***	26 ± 7***
α-MNE	0.1	113 ± 5	120 ± 10	1.5 ± 1.5 (N.S.)	2 ± 1 (N.S.)
	1	117 ± 4	120 ± 5	2.5 ± 2.5 (N.S.)	1.5 ± 1.5 (N.S.)
	10	115 ± 3	150 ± 10	5 ± 1 (N.S.)	3 ± 3 (N.S.)
Cirazoline	0.01	136 ± 9	158 ± 7	8 ± 2*	1.5 ± 1.5 (N.S.)
	0.1	128 ± 9	147 ± 12	11 ± 1**	2.5 ± 2.5 (N.S.)
	1	119 ± 13	135 ± 13	20 ± 1***	4.5 ± 4.5 (N.S.)
ST 587	1	113 ± 12	140 ± 10	4 ± 1.5 (N.S.)	2 ± 1.5 (N.S.)
	3	116 ± 9	130 ± 10	6.5 ± 2*	2 ± 1.5 (N.S.)
	10	135 ± 15	120 ± 10	31 ± 5**	8 ± 5 (N.S.)

* $P < .05$; ** $P < .01$; *** $P < .001$.

rmore, this result shows that a selective *alpha*-2 agonists s not necessarily induce hypotension when applied at the in site of action of clonidine. We find a somewhat symmetal situation within the medulla oblongata. In fact, according Kubo and Misu (1981), De Jong and Nijkamp (1976) and idberg and De Jong (1977), *α*-MNE has a hypotensive effect en administered directly into the medial part of the nucleus ctus solitarii, a dorsal medullary structure (fig. 2), where it nulates a vasodepressive center, whereas clonidine in the ne place has virtually no effect on arterial pressure. It is, refore, impossible to relate the hypotensive effect of these compounds to a single action mechanism such as the mulation of postsynaptic *alpha*-2 adrenoceptors.

In another series of experiments, we observed that both azoline and ST 587, which have the lowest *alpha*-2 adrenotor selectivity of the whole series of *alpha*-adrenergic agots, can produce dose-dependent hypotension, when administered into the region of the NRL, similar to that of clonidine. appears, therefore, that the relative affinity of the imidazoles for the *alpha*-2 adrenergic receptors does not influence eir hypotensive effect. In fact, we report here that cirazoline as active as clonidine when injected in the NRL region hough its affinity for *alpha*-2 adrenoceptors is one-tenth of at of clonidine (Rouot *et al.*, 1982).

Our results obviously only apply to the NRL inasmuch as razoline and ST 587 are known to have no hypotensive effect nen administered systemically or in the vertebral artery (De nge *et al.*, 1981). The cardiovascular effects of a compound lministered systemically or even into the whole brain may ffer from those obtained when the substance is injected in a rticular brain region for several reasons. A compound may t differently on several brain structures; thus, some drugs ay have a hypertensive influence within the forebrain which ay mask a vasodepressive action originating in the brain em. This may occur with cirazoline and ST 587. Conversely, onidine mainly depresses medullary structures, whereas it has weak vasopressive influence within the forebrain (Bousquet nd Guertzenstein, 1973; Trolin, 1975). One can also suggest at cirazoline and ST 587 might have important peripheral asoconstrictive action which would mask their central hypomsive effects. Further experiments are needed to clarify these oints.

We have observed that among the drugs we have tested so ar, those containing an imidazoline ring (clonidine, cirazoline, T 587) are hypotensive when administered directly into the RL region, in contrast to the catecholamines (*α*-MNE and orepinephrine) even when they have a selectivity for the lpha-2 adrenoceptors (*α*-MNE). There are parallels here with he observations of Ruffolo on the peripheral *alpha* receptors.)n the basis of structure-activity relationship, Ruffolo showed hat the catecholamine-sensitive sites have different structural equirements than those for the imidazolines in smooth muscle Ruffolo *et al.*, 1980, 1982, 1983; Ruffolo and Waddell, 1982). or instance, in the guinea-pig aorta and the field-stimulated uinea-pig ileum, the isomeric activity difference between the nantiomers of 2(3-4-trihydroxybenzyl) imidazoline is relaively small compared to that observed with phenylethylamines, uggesting that the stereochemical requirements made by peipheral *alpha* adrenoceptors for imidazolines may be less than hose for the catecholamines (Ruffolo *et al.*, 1983). The results onfirm the authors' earlier observations which suggest that he imidazolines and the phenylethylamines interact differently

with the peripheral *alpha* adrenoceptor. Similarly, Mottram and Thakar (1983) detected in the field-stimulated guinea-pig ileum such a difference in activity between clonidine and *α*-MNE that the former could under certain conditions become an antagonist of the latter. On these models, the effects of stimulating these two types of sites are the same, namely contraction. Our results suggest that in the NRL region, there are imidazoline-preferring sites, the stimulation of which may inhibit a vasopressive structure. Contrary to what has been shown in the blood vessels, there do not seem to be any catecholamine-preferring sites with a cardiovascular function similar to that of the imidazoline-preferring sites in this medullary region.

In conclusion, we report here that, after injection into the NRL, an important site for the hypotensive action of clonidine, *α*-MNE a selective *alpha*-2 agonist, has no cardiovascular effect, whereas cirazoline and ST 587, like clonidine, have a hypotensive effect. These results confirm that the central mechanism of action of *α*-MNE, postulated to be the active metabolite of *α*-methyldopa, differs from that of clonidine. Not only are selective *alpha* agonists inactive on the clonidine action site, but potent *alpha*-1 agonists even have hypotensive effects there. Our results demonstrate that clonidine-like substances may stimulate imidazoline-preferring sites in the NRL region. These sites differ from the classical *alpha*-2 adrenergic receptor because catecholamines with high *alpha*-2 adrenergic affinity do not stimulate these receptors and also the affinity for the *alpha*-2 adrenoceptors of imidazolines does not influence their effects. However, the nature of these receptors remains unclear.

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